UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 04-JUN-2013

SUBJECT: **Glyphosate.** Review and generation of Data Evaluation Records

PC Code: 417300
Decision No.: 470197
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0056604
MRID No.:44320610, 44320612

DP Barcode: D405651
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 1071-83-6
40 CFR: 180.364

FROM: Monique M. Perron, S.D.
Toxicologist, Risk Assessment Branch I (RABI)
Health Effects Division (HED) (7509P)

Monique Perron

THROUGH: Dana Vogel, Deputy Director
Health Effects Division (HED) (7509P)

TO: Carissa Cyran, Risk Review Manager
Pesticide Re-evaluation Division

I. CONCLUSIONS

RABI has reviewed the acute and subchronic neurotoxicity studies for glyphosate and they are acceptable/guideline studies.

II. ACTION REQUESTED

Acute and subchronic neurotoxicity studies for glyphosate have been submitted. RABI was asked to review and prepare DERs for these studies.

Primary Reviewer: Monique Perron, S.D. **Signature:** Monique Perron
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** 6/4/13

Secondary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** 06/04/13

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0056604

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [§81-8]; OECD 424.

DP BARCODE: 405651

P.C.CODE.: 417300

MRID NO.: 44320610

TEST MATERIAL (Purity): Glyphosate technical (95.6% w/w)

SYNONYMS: *N*-(phosphonomethyl)glycine

CITATION: Horner, S.A. (1996) Glyphosate acid: acute neurotoxicity study in rats. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. March 11, 1996. MRID 44320610. Unpublished.

SPONSOR: Zeneca Inc., Agricultural Products, Wilmington, DE

EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRID 44320610), groups of fasted (24 hours), approximately 42 day old Alpk:APfSD rats (10/sex/dose) were given a single oral dose of glyphosate (purity 95.6% w/w, batch #P24) in deionized water at doses of 0, 500, 1000, or 2000 mg/kg bw and observed for 2 weeks. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in all animals in week -1, on day 1 (approximately 6 hours after dosing), day 8 and day 15. At study termination, 5 animals/sex/dose were euthanized and perfused. Of the perfused animals, the control and highest dose groups were used for neuropathological examinations and brain and peripheral nervous system tissues subjected to histopathological evaluation.

Administration of a single dose of glyphosate produced treatment-related clinical signs of general toxicity at 2000 mg/kg bw. At approximately 6 hours after dosing on day 1, three females in the 2000 mg/kg bw dose group were observed with decreased activity, subdued behavior, hunched posture and/or hypothermia. Diarrhea was also seen in an additional female at this dose. Full recovery was established by day 2. These clinical signs do not reflect signs of neurotoxicity and are mostly likely associated with administration of excessively high doses of glyphosate. There were no treatment related effects observed on mortality, body weight, or brain weight. Similarly, neuropathological and histopathological examinations displayed no treatment-related effects. Functional observational battery and motor activity testing revealed no treatment-related effects. Although overall motor activity was lower than controls at 2000 mg/kg bw for both sexes on day 1, these differences were not statistically significant or dose-dependent.

The lowest-observed-adverse-effect level (LOAEL) for this study was 2000 mg/kg bw based on clinical signs of general toxicity (decreased activity, subdued behavior, hunched posture, hypothermia and diarrhea). The no-observed-adverse-effect-level (NOAEL) for this study is 1000 mg/kg bw.

CLASSIFICATION

This neurotoxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

COMPLIANCE:

Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

Primary Reviewer: Monique Perron, S.D. **Signature:** Monique Perron
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** 6/4/13

Secondary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** 06/04/13

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0056604

STUDY TYPE: Subchronic Neurotoxicity (feeding; rat)
OPPTS 870.6200b [§82-7], No OECD guideline

DP BARCODE: 405651

P.C.CODE.: 417300

MRID NO.: 44320612

TEST MATERIAL (Purity): Glyphosate technical (95.6% w/w)

SYNONYMS: *N*-(phosphonomethyl)glycine

CITATION: Horner, S.A. (1996) Glyphosate acid: subchronic neurotoxicity study in rats. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. March 11, 1996. MRID 44320612. Unpublished.

SPONSOR: Zeneca Inc., Agricultural Products, Wilmington, DE

E XECUTIVE SUMMARY:

In a subchronic neurotoxicity study (MRID 44320612) glyphosate (purity 95.6% w/w, batch #P24) was administered to 12 Alpk:APfSD rats/sex/group in the diet at dose levels of 0, 2000, 8000, or 20000 ppm (equivalent to 0, 155.5, 617.1, 1546.5 mg/kg bw/day for males and 0, 166.3, 672.1, 1630.6 mg/kg bw/day for females) for 13 weeks. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in all animals at weeks -1, 1, 5, 9, and 14. At study termination, 6 animals/sex/group were euthanized and perfused. Of the perfused animals, the control and highest dose groups were used for neuropathological examinations and brain and peripheral nervous system tissues subjected to histopathological evaluation.

Overall mean body weight ($p<0.05$) and food utilization ($p<0.01$) were reduced in males receiving 20000 ppm glyphosate with no treatment related effect on food consumption. Group mean bodyweight was also lower than controls in males receiving 8000 ppm from weeks 6 to 14 (not statistically significant). There were no treatment related effects observed on mortality, clinical signs, or brain weight. Functional observational battery and locomotor activity testing revealed no treatment-related effects. Neuropathological and histopathological examinations of the peripheral and nervous system did not yield any treatment-related effects from glyphosate administration.

The lowest-observed-adverse-effect level (LOAEL) was not observed. The no-observed-adverse-effect-level (NOAEL) for this study is 20000 ppm (1546.5 and 1630.6 mg/kg bw/day for males and females, respectively).

CLASSIFICATION

This neurotoxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200; OECD 424).

COMPLIANCE:

Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.